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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,665	NIELSEN ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/23/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above claim(s) *1-53 and 59-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Aditi Dutt.

Status of Claims

1. The amendment filed on 23 August 2007 has been entered into the record and has been fully considered. Claims 54-58 are amended. New claims 69-70 are added.

2. Claims 54-58, drawn to a method for protecting, maintaining or enhancing the viability of a responsive cell by administering a tissue protective cytokine in vivo or ex vivo, are under consideration in the instant application. New claims 69 and 70 do not fall under the scope of the currently elected invention and species, therefore, is withdrawn.

3. It is to be noted that the restriction requirement is deemed proper and is therefore made FINAL.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed on 23 August 2007, have been fully considered. New grounds of objection and rejection are as follows.

Response to Amendment

Withdrawn objections and/or rejections

6. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (23 August 2007).

7. Upon consideration of Applicant's arguments which were persuasive, rejection of claims 54-58, under 35 USC § 102(b), is withdrawn.

8. Upon consideration of amendments to claims, rejection of claims 54-58 under 35 USC § 112, 2nd paragraph is withdrawn.

Claim rejections/objections maintained/new grounds of rejection

Claim objection

9. Applicant's arguments with regards to non-elected subject matter and dependency from non-elected claims is considered but not found to be persuasive. The objections to claims 56-58 will thus be maintained on record until appropriate correction is made.

Claim Rejections

10. Double Patenting

Applicants have requested that the rejections be held in abeyance until the indication of allowable subject matter is presented. The rejections will be maintained of record until the submission of terminal disclaimers.

35 U.S.C. § 112, first paragraph – Lack of enablement

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. The rejections of claims 54-58, are applied to the amended claims, for reasons of record in the Office Action dated 23 February 2007.

13. Applicants disagree with the Examiner's contention that the full scope of the claims is not enabled for reasons explained below. Applicant's arguments are found to be persuasive in part, because of narrowing the claims to recite "responsive cell", thus the lack of enablement for the recitation "any cell" is withdrawn.

A) Protection or Rejuvenation of tissue following tissue injury

14. Applicant argues that numerous detailed examples are provided in the specification as regards tissue injury, tests to determine the ability of tissue protective cytokines in restoring cognitive function and tissue rejuvenation.

Applicants assert their contention by citing examples in the specification. Additionally Applicants add that Villa et al. tests the ability of S100E mutein to improve neurological function with stroke. Moreover, Applicants argue that prevention can either be interpreted as "reduced tissue injury" or "total prevention", and that there is no "legal requirement that every embodiment within the scope of the claim be demonstrated by working examples". Applicants thus believe that the instant specification has enabled to one of ordinary skill to make and use the full scope of the invention without undue experimentation.

15. Applicant's arguments directed to the claimed invention have been fully considered but have not been found to be persuasive. Although the art recognizes in vivo and in vitro protective effect of erythropoietin (EPO) on ischemic injury models and certain immune mediated inflammatory responses using EPO and EPO recombinant variants like K45D, R103E, R150E, and S100E, the art and the instant specification fail to provide guidance or sufficient scientific basis to use any tissue reactive cytokine for any tissue injury. As stated in the previous Office Action, Applicant's invention is predicated on findings, that EPO has neuroprotective effect as well as being able to reduce retinal ischemic damage, and Applicant extrapolates these findings into a method for protecting, maintaining or enhancing the viability of a responsive cell, tissue or organ using any recombinant variant or EPO mutein. Moreover, the sparing of neuronal tissue mass lost to injury indicates only that EPO is capable of reducing inflammation-associated neuronal cell death, such as apoptosis or necrosis, but does not go

so far as to implicate EPO as being able to induce new cellular growth, which would be necessary to restore or rejuvenate tissue or tissue function. Undue experimentation would be required to rejuvenate or prevent a tissue injury using any recombinant tissue protective cytokine or EPO mutein.

16. Applicants cite "Brines Declaration", wherein Dr. Brines tested animal models of diabetic peripheral neuropathy SOD mice (used as a model for amyotrophic lateral sclerosis) for motor degeneration and suggests that all neurodegenerative diseases exhibit neuronal loss due to oxidative damage. In essence, the declaration asserts "the ability of EPO to protect against and alleviate the symptoms of neurodegenerative diseases irrespective of the primary cause of the individual neurodegenerative disease".

17. The declaration is considered but not found to be persuasive because although a common pathway, such as via oxidative damage, could result in all neurodegenerative diseases, different cell types are involved in long term chronic neurodegenerative illnesses, that will determine the overall responsiveness to various therapeutics, leading to unpredictability and undue experimentation. Furthermore, these diseases have other causes also, and so long as the other causes are not identified and corrected, the effect of EPO will be inconsistent and unpredictable. Because neurodegenerative diseases are multifaceted, injuries in such diseases could be due to various reasons, whereby more than one pathway may be disabled or degenerated. Based on the lack of definitive information on

the pathology and treatment of such diseases, the outcome is dismal and unpredictable.

B) Any Mutein

18. Applicants disagree on the Examiner's contention for any mutein recombinant tissue protective cytokine, reason being that Applicant elected the species of SEQ ID NO: 62 in response to the restriction requirement. Applicants further assert that to one of ordinary skill in the art, the instant specification has provided sufficient guidance to make and use the mutein recombinant tissue protective cytokine (pages 92-101). Applicant states the use of routine DNA technology and bioassays, for the generation and testing of mutants for tissue protection, none of which would prove the experimentation as undue. Applicants have supported their contention providing large number of case laws.

19. Applicant's arguments have been fully considered but have not been found to be persuasive. Examiner acknowledges that SEQ ID NO: 62 was elected, However, the claims broadly read on any recombinant tissue protective cytokine. As stated in the previous Office Action (page 13); (emphasis added by examiner)

With regard to the claim breadth, the standard under 35 U.S.C. § 112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As

such, the broadest reasonable interpretation of claims 54-55 is an ex vivo method encompassing the use of **any mutein recombinant tissue protective cytokine**, and claim 56 is directed to an ex vivo method encompassing the use of **any recombinant tissue protective cytokine** lacking at least one particular activity normally associated with erythropoietin. The broadest reasonable interpretation of claims 57-58 is of a method of protecting against or preventing any tissue injury *in vivo,* or a method of restoring or regenerating new tissue or tissue function *in vivo,* using **any recombinant tissue protective cytokine** so long as it lacks at least one commonly associated erythropoietic activity.

20. Furthermore, the arguments presented by Applicant with regards to the making and using of muteins is persuasive in part. While it is accepted that routine technology and bioassays can be run without causing undue experimentation, the testing of the numerous mutants for tissue protection would entail undue numbers of trial and error attempts, because tissue responsiveness will vary depending on the receptor binding affinity, specificity, etc. of the muteins. Additionally, the testing will involve different doses for different mutein molecules. Lastly, the in vitro testing using cell lines, does not parallel the in vivo protection, wherein the injury can arise due to various causes. The examiner takes no issue with the case laws.

21. Specifically, proper analysis of the Wands factors was provided in the previous Office Action (see pages 9-17, of the Office Action dated 23 February 2007). Therefore, in view of the breadth of the claims encompassing the use of molecules with no precise structural requirements, the lack of adequate guidance or working example(s) or data or evidence supporting a therapeutic effect of EPO

molecules on the broadly claimed chronic and/or degenerative diseases or disorders, or guidance on their use, the unpredictability in the art of treatment of chronic and neurodegenerative disease, the unpredictability in the art of biological effects of modifying EPO molecules, and the complex nature of the invention, one of skill in the art would find that undue experimentation would be required to practice the claimed invention.

112-1st paragraph – Written Description

22. The rejections of claims 54-58, are applied to the amended claims, for reasons of record in the Office Action dated 23 February 2007.

23. Applicant argues that as per restriction requirement, SEQ ID NO: 62, was elected as the species of tissue protective cytokine, to which the Examiner had acknowledged. Moreover, Applicant states that the specification provides sufficient disclosure on the various muteins listed in Example 3. Applicant further asserts that the amino acid regions (44-51 and 100-108) are required for EPO activity, and mutations in these regions yield a mutein recombinant EPO having reduced erythropoietic activity", thereby alleging that the rejection under 35 USC 112, first paragraph is improper, thus should be withdrawn.

24. Applicant's arguments have been fully considered but have not been found to be persuasive, because of the breadth of the claims that fail to recite a single species of the mutein. As stated in the previous Office Action, the methods require the use of cytokine molecules that are defined only by broad functional

limitations, the claims encompass a method of using a genus of cytokine molecules. However, the scope of the claims encompasses cytokine molecules that are not limited to the elected species, SEQ ID NO: 62 (S100E variant), or to the particular species of Examples 17 and 18. Furthermore the muteins listed on pages 32-35, and 47-49, include muteins with mutations outside amino acid residues of 44-51 and 100-108 of the native EPO, that must be conserved for the EPO activity, as mutations in this region can result in decreased erythropoeitic activity. As stated in the previous Office Action, it is reiterated as follows:

> Accordingly, there is no means by which the artisan, given any ot these cytokine molecules, would know whether it was a member of the genus that could be used in the claimed methods. The instant disclosure of the several specific mutein EPO species does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. Therefore, the claims are directed to subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed genus of molecules.

New Rejections/Objections

Claim Objection

25. It is noted that SEQ ID NO: 62 and SEQ ID NO: 5 are identical.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

26. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

27. Claims 54-58 are rejected under 35 U.S.C. 102(e) as clearly anticipated by Brines et al. (International Publication No WO 02/053580 A2, filed on 28 December 2001, with a prior filing date for US Patent application number 09/753,132, of 29 December 2000).

28. Claims 54-58, drawn to a method for protecting, maintaining or enhancing the viability of a responsive cell, tissue or organ, by administering a recombinant

tissue protective cytokine in vivo or ex vivo, wherein the cytokine lacks at least one activity.

29. Brines et al. teach methods for protecting or enhancing an erythropoietin responsive cell, tissue or organ in vivo, in situ or ex vivo, comprising the administration of modified EPO comprising at least one modification in amino acid sequence as compared to native EPO (page 4, para 2), and which is non-erythropoietic or lacking an activity of EPO (claims 59-61), therefore, inherently does not affect bone marrow. Brines et al further teach the treatment or protection by the administration of EPO to mammals having various disorders like heart failure, retinal detachment or trauma, etc. (Table, page 46-50). Thus Brines et al. anticipate the claimed invention.

30. Claims 54-57 are rejected under 35 U.S.C. 102(b) as clearly anticipated by Campana et al. (Int J Mol Med 1(1):235041, 1998; abstract).

31. Claims 54-58, drawn to a method for protecting, maintaining or enhancing the viability of a responsive cell, tissue or organ, by administering a recombinant tissue protective cytokine in vivo or ex vivo, wherein the cytokine lacks at least one activity.

32. Campana et al. teach a method of exerting neurotrophic effect by preventing cell death (i.e. enhancing viability) and inducing differentiation in human and mouse neuroblastoma cells (SR-N-MC and NS20Y respectively),

comprising exposing the cells to a 17-mer peptide sequence (epopeptide AB) in EPO, and demonstrating neurotrophic effects of the peptide (abstract). Campana Det al. further teach that epopeptide AB does not promote the proliferation of erythropoietic cell lines, thereby indicating a lack of erythropoietic activity of increasing hematocrit. It is to be noted that epopeptide AB is a peptide that has resulted from the deletion of amino acids from the native EPO sequence, thereby fitting into the definition of "recombinant" in the instant specification (see pages 3 and 4, lines 33-34, 1-4 respectively). Lastly, since the method is conducted in a culture medium, the tissue reactive cytokine will inherently be unable to affect the bone marrow. Thus Campana et al. anticipate the claimed invention.

Declarations

33. Several declarations were submitted under Rule 130, 131 or 132 Affidavits. However, no reference to the declarations was made in Applicant's response.

Conclusion

34. No claims are allowed.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571)

272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

36. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

37. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
22 December 2007

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER